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GENERALIZED INTESTINAL POLYPOSIS AND MELANIN SPOTS OF THE ORAL MUCOSA, LIPS AND DIGITS*

A Syndrome of Diagnostic Significance

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IN 1944, a brief report was made by one of us¹ regarding the association, in 2 patients, of a distinctive type of melanin pigmentation of the oral mucosa, lips and digits with intestinal polyposis.

Since then 10 cases, including the 2 referred to above, have been collected from five different hospitals and are reported here in detail along with a review of pertinent literature and a discussion of the significance of this syndrome.

CASE REPORTS

CASE 1. A 14-year-old American schoolgirl entered the Fifth Medical Service of the Boston City Hospital on March 11, 1939, with the complaint of persistent diarrhea of 6 weeks' duration. There were five or six watery bowel movements each day. No mucus, blood or fat was ever noted in the stools. Intermittently during this period there were bouts of vomiting. Her appetite was good. There was no pain, but the patient noted frequent loud gurgling noises in the abdomen. During the present illness there was a 4-pound weight loss.

Twice in 1933 she had been operated upon at another hospital for intussusception and intestinal obstruction. On the second occasion a portion of the ileum was resected. Polyps of the stomach, ileum and sigmoid were found at that time. So far as could be ascertained the family history was non-contributory. The parents believed the spots on the lips had been present since early childhood and apparently had not changed over the years.

Physical examination revealed a thin, rather undernourished patient appearing acutely ill. The hair and irides were dark brown. The skin was pale. On the face, concentrated about the mouth, and on the lips and oral mucous membrane were numerous small, brown-black spots. Similar areas of pigmentation were noted on the dorsal surface of the fingers (Fig. 1). A few pigmented spots were also observed on the toes. There were two small patches of vitiligo on the back. The heart and lungs were normal. The abdomen was moderately distended, with tenderness over the upper half. Loud borborygmi were present. The liver edge was palpable two fingerbreadths below the right costal

margin. There was slight clubbing of the fingers and toes. Examination otherwise was negative.

The blood pressure was 85/40.

Examination of the blood showed a red-cell count of 2,410,000, with a hemoglobin of 70 per cent, and a white-cell count of 7400, with a normal differential count. The red cells were slightly hyperchromic and macrocytic. The blood Hinton test was negative. The urine was normal. The stools were loose, brown and guaiac negative. Gastric analysis revealed 24 units of free hydrochloric acid and 46 units of total acid. Barium-enema study by the double contrast method showed multiple negative shadows consistent with polyps scattered throughout the large intestine. Many small clusters of two to four polyps in the sigmoid and rectum were directly visualized on sigmoidoscopic examination. No areas of pigmentation were noted.

A regimen of symptomatic measures supplemented by frequent administration of liver extract and iron resulted in disappearance of the diarrhea, with improvement in weight and a subjective feeling of well-being, and with an increase in the hemoglobin to 88 per cent and in red-cell count to 3,300,000. The patient was discharged after 6 weeks in the hospital.

On August 19, she was readmitted to the hospital because of a return of diarrhea during the preceding month. The findings were as on the previous entry, and satisfactory improvement resulted from similar therapy. She was discharged in 3 weeks.

Lobar pneumonia due to a Type I pneumococcus necessitated readmission on November 21. There was no bacteremia. Treated with sulfapyridine and general supportive measures, she failed to show any response and died on December 1.

At autopsy pigmentation of the skin as previously described was noted.

Death was due to lobar pneumonia of the right lung. The pleural cavity was normal, as were the heart and pericardial cavity.

The esophagus was normal. The mucosa of the stomach bore three soft pedunculated polyps ranging from 1.5 to 2.5 cm. in diameter, one lying just below the cardiac orifice, a second on the greater curvature, and a third near the pyloric sphincter of the stomach. The mucosa otherwise was normal, as was the duodenum. The jejunum and ileum showed some brownish-black, granular pigment along the edge of the mucosal folds. In addition, a polyp occurred every 50 to 60 cm. These averaged 1 to 2 cm. in diameter and were attached to pedicles that were 0.5 to 1.0 cm. in length. The terminal ileum contained the largest polyp in the gastrointestinal tract; this measured 4.5 cm. in diameter. One mulberry-like polyp measuring 1.5 cm. was present in the sigmoid portion of the large intestine.

The liver weighed 1960 gm. It was of normal color and consistence and on section bore the usual geographic markings. Microscopical examination showed lipid vacuolization of the liver cells at the central portions of the lobules.

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The spleen weighed 260 gm. Its capsular surface was dark purple and wrinkled. Microscopically the features of congestion were prominent. Both adrenal glands were considerably smaller and thinner than normal, but showed no abnormality on microscopical examination. The uterus appeared smaller than usual; the left ovary contained two small cysts.

The vertebral bone marrow showed granulocytes in all phases of development; numerous stem cells were present.



FIGURE 1. Appearance of the Patient in Case 1.

Note the spots distributed thickly on and around the lips and sparsely over the bridge of the nose. Highlight in the photograph prevents the clear view of the spots on the fingers of the right hand.

There were moderate numbers of nucleated red blood cells and occasional scattered hemosiderin-filled macrophages.

Microscopical examination of the jejunal mucosa showed the tips of many villi to be club shaped and filled with macrophages containing large clumps of hemosiderin. Well differentiated adenomatous cells comprised the mucosal polyps.

CASE 2. A 39-year-old housewife of Italian-French descent entered the Boston City Hospital on October 22, 1939. For the previous 9 months she had noted increasing constipation requiring frequent enemas. In addition there was intermittent rectal bleeding. Twenty-four hours prior to entry, a mass, which was very painful and bled on attempts at replacement, protruded from the rectum.

Twenty years previously the right fallopian tube and ovary had been removed because of chronic pelvic disease. Five years before the final admission a cholecystectomy was performed after indigestion and pain in the right upper quadrant of the abdomen of 1 year's duration. Three years later the patient was observed in the hospital because of recent onset of anorexia, nausea and vomiting. A gastrointestinal x-ray series revealed irregularity of the stomach and displacement of the duodenal cap, interpreted as being due to postoperative perigastric and periduodenal adhesions.

The patient's parents and husband were living and well. She had had 4 miscarriages. There were 2 healthy children. A first cousin (Case 4) and this cousin's daughter (Case 5) both suffered from complaints referable to the gastrointestinal system. There was no familial tendency to freckles.

Physical examination revealed a well developed and fairly well nourished woman. There were numerous brown and bluish-brown pigmented spots on the face about the eyes

and the mouth, on the lips and gums and on the fingers and toes. These averaged 1 to 3 mm. in diameter (Fig. 2). There was no pigmentation elsewhere on the body. The hair was black, and the eyes dark brown. The head was normal. The lungs were clear. The heart was not enlarged, and the rate was 80, with a regular rhythm and sounds of good quality. A soft systolic murmur was audible at the apex. There were no thrills or rubs. The abdomen was soft and not distended; in the lower abdomen there was moderate tenderness, and a poorly defined movable mass was palpated in the right lower quadrant. The rectum was found to be prolapsed and external hemorrhoids were visible. There was slight clubbing of the fingers.

The blood pressure was 108/70.

Examination of the blood showed a red-cell count of 4,160,000, with a hemoglobin of 85 per cent, and a white-cell count of 7500, with a normal differential count. The blood Hinton test was negative, as was examination of the urine. The stools were tarry black and gave a ++++ guaiac reaction. A gastrointestinal x-ray series revealed multiple polyps of the small and large intestine.

A series of operations was embarked upon: ileostomy, partial colectomy, fulguration of polyps in the rectosigmoid and anastomosis between the ileum and rectosigmoid. In-



FIGURE 2. Appearance of the Patient in Case 2.

Note the density of the spots on the lips. Melanin spots on the fingers are readily noticeable in this photograph.

Initially, the patient showed some improvement, but after the last procedure there was considerable intraperitoneal and wound infection, and evidence of the development of a fecal fistula to the abdominal wall. She began to fail rapidly in weight and strength and died on March 14, 1940.

At autopsy pigmentation of the skin as previously described was noted. Examination of the pericardial cavity was negative. The heart was normal in size and weight. The aortic valve was slightly thickened; the right and posterior cusps were fused along the entire length of the commissure. The tricuspid valve contained only two well formed leaflets and appeared identical with the mitral valve. The foramen ovale and ductus arteriosus were closed.

Examination of the pleural cavity was negative. The lungs were of normal size and weight. The right lung contained an azygos lobe.

The peritoneal surfaces were grayish yellow, with a marked amount of thin, foul-smelling exudate. A pelvic abscess was found at the site of anastomosis of the ileum and rectosigmoid. The superior mesenteric artery originated from the celiac axis. The stomach contained a 1.0-cm. sessile polyp in the middle portion of the greater curvature; the mucosa was otherwise normal. In the duodenum the mucosa contained 10 pedunculated polyps varying from 0.8 to 2.0 cm. in diameter. The pedicles were from 0.5 to 3.0 cm. in length and all were approximately 3 to 5 mm. in thickness. There was 1 small polyp of the jejunum, and 8 in the ileum, all being pedunculated and varying in size as those described.

the duodenum. The entire mucosa of the small intestine was brown gray, giving the appearance of fish skin. The rectum contained several cherry-red fungating polyps, 2 or 3 cm. in size. The liver, spleen, kidneys and adrenal glands were normal.

Microscopical examination of the jejunal polyp showed it to be composed of acini of tall columnar cells, some of which were goblet cells, radiating from a fibromuscular pedicle.

CASE 3.* A 22-year-old woman was admitted to the Rhode Island Hospital, Providence, Rhode Island, on November 16, 1936, because of periodic abdominal pain of 3 months' duration consistent with the diagnosis of intussusception.

The family and past histories were irrelevant. No information about the duration of the oral pigment spots in the patient or their possible presence in her forebears was available.

Physical examination of the mouth and face revealed many small melanin spots on the lips and on the mucosa of the inside of the mouth (Fig. 3). Information regarding spots on the hands and feet was not available.

At operation an intussusception of the terminal ileum due to a polyp was found, and a hard mass in the small intestine about 30 cm. from the cecum proved to be an adenocarcinoma of the ileum. Resection of this lesion and side-to-side anastomosis were done, with good results and an uneventful



FIGURE 3. *Appearance of the Buccal Mucosa in Case 3.*
Note the size and distribution of melanin spots on the buccal mucosa. Those on the lips are readily seen despite the presence of lipstick. Relatively few are present on the skin about the mouth. (Photograph published through the courtesy of Dr. F. Ronchese, of Providence, Rhode Island.)

recovery. Polyps of the stomach were said to have been present also.

The patient was seen periodically for follow-up study. In August, 1937, another operation was performed because intestinal obstruction was suspected. A band of tissue was excised. In January, 1939, she again had an episode suggestive of intestinal obstruction. In July, 1940, she was operated upon for recurrent abdominal pain. Large polyps were found in the stomach near the pylorus and in the ileum, and appropriate surgical therapy was applied. After this she was symptom-free for 2 months.

In November abdominal pain and obstructive signs recurred. At operation intussusception was seen, and polyps of the stomach, jejunum and ileum noted. In March, 1942, intussusception due to small-gut polyposis again necessi-

tated operation; at this time the additional diagnosis of polyposis of the large intestine was added to the patient's record. At the last report in September, 1944, the patient was working regularly and free of complaints.

CASE 4. A 30-year-old housewife of Italian ancestry was admitted to the Boston City Hospital on November 2, 1935. She complained of mid-abdominal pain, intermittent and colicky, of 2 days' duration. Two years previously there had been two similar attacks, which had subsided spontaneously. There was a history of chronic constipation. Three years previously an appendectomy had been performed.

The family history was irrelevant, except for the occurrence of pigmentation of the face, similar to the patient's, in her



FIGURE 4. *Pigmentary Pattern Similar in Mother (Case 4) and Daughter (Case 5).*
Note the main distribution in each on and about the lips.

father and her paternal grandmother, as well as in her own daughter (Case 5) and her first cousin (Case 2).

Physical examination revealed a well developed and well nourished woman who appeared acutely ill. The temperature was 99°F. There were numerous small brown-black pigmented areas on the lips, oral mucosa and nose (Fig. 4), and a few on the fingers and toes. The lungs were clear. The heart was normal. The blood pressure was 120/78. Abdominal examination revealed tenderness immediately above and to the left of the umbilicus, where a small, firm mass was intermittently palpable. There was no muscle spasm. The white-cell count was 15,000.

At laparotomy, performed shortly after admission, an intussusception of the ileum was readily discerned. This was reduced easily, and the darkened color of the intestine improved promptly. A small dimple was seen on the serosa of the ileum at the origin of the intussusception. At this point a mass was palpable within the lumen from which a walnut-sized polyp was excised. The patient made a prompt and satisfactory recovery postoperatively.

Examination of the surgical specimen showed it to consist of a soft, mucosa-covered papilloma with a small pedicle. The mucosa was intact and normal in appearance. The cut surface revealed a smooth, gray appearance. Microscopically, the specimen had the characteristics of a benign polyp.

CASE 5.† A 9-year-old girl of Italian ancestry was admitted to the Children's Hospital of Boston on December 10, 1937, with the complaint of abdominal pain.

For the previous 2 years the child had had recurrent bouts of severe, crampy abdominal pains localized at the umbilicus.

*Reported through the courtesy of Dr. Francesco Ronchese, of Providence, Rhode Island.

†This case and Figure 4 and 5 were made available through the courtesy of the Children's Hospital, Boston, Massachusetts.

They had never been associated with dietary indiscretions or irregularity of the bowels. The pains had been paroxysmal, lasting a few minutes and recurring in a few minutes, usually disappearing entirely after 1 or 2 hours. Occasionally, vomiting had been present with these episodes, but no bloody, tarry or mucus-containing stools had been noted. Typically, the patient was well immediately before and immediately after each attack, and on examination by various physicians and at outpatient clinics after an attack no abnormality had been found.

One hour before this hospital admission the patient again suffered a typical recurrence of crampy abdominal pain, which differed only in that it seemed much more severe than on previous occasions. Instead of disappearing, this pain kept recurring in stronger paroxysms every 1 or 2 minutes, making the child scream with pain. A few minutes after the



FIGURE 5. Close-up Photograph in Case 5, Showing the Density of the Melanin Spots on the Lips and about the Mouth.

onset of this illness she began to vomit bile-stained material. Nothing was passed by rectum.

The patient had been a full-term, normal baby. She had been examined on several occasions in the Outpatient Department during the preceding 3 years for attacks of bronchitis and after previous attacks of abdominal pain. The past history was otherwise noncontributory. Her parents were living; the mother (Case 4) had undergone an abdominal operation for intussusception 2 years previously. One brother, 8 years of age, was living and well. Another sibling had been born dead 11 years previously. The patient's mother, and the latter's father and paternal grandmother had all had similar pigmentation of the face about the mouth. Unfortunately, information concerning polyposis in these ancestors was unobtainable.

Physical examination revealed an acutely ill girl. There were numerous blue-brown to black small spots on the face, concentrated about the mouth and on the mucosa of the lips and mouth (Fig. 4 and 5). The hair and irides were dark brown. Examination of the heart and lung was negative. The abdomen was not distended, but there was moderate fullness in the left upper quadrant. No direct spasm could be elicited, but intermittently there was tenderness over a transiently palpable tumor in the left upper quadrant. This tumor appeared to be fairly movable in all directions and measured 10 by 5 cm. The liver edge was felt 1 cm. below the costal margin. Rectal examination was negative. The white-cell count on entry was 20,150.

Shortly after examination a laparotomy was performed. A jejunoileal intussusception was promptly noted and was reduced. A walnut-sized tumor could be palpated at the site of intussusception, and on opening of the intestine a polyp was removed. *Staphylococcus aureus* septicemia, with pneumonia, empyema and peritonitis developed, and the patient died on January 2, 1938.

At autopsy, in addition to the pigmentation previously noted, there was a generalized petechial eruption. Bilateral bronchopneumonia and empyema were present. The abdominal cavity contained a large amount of brown fluid.

The mucosa of the stomach was thrown up into prominent longitudinal rugae, and on the tips of these rugae four polypoid formations were noted. These varied from mere mucosal elevations to one pedunculated polyp 2 cm. in diameter; they were pinkish white and slightly lobulated. The entire small intestine contained numerous polyps of varying size, most of them about the size of a pea and many with pedicles, but occasional ones showing a sessile type of base. These were attached to the intestinal villi. The appendix was 10 cm. long, with a reddish-black, bulbous tip. It was retrocecal in position and bound down in an appendiceal abscess. There was no abnormality of the large intestine. The mucosa of the rectum contained a polyp about 2 cm. in diameter. A total of twenty polyps of the gastrointestinal tract were counted. The adrenal glands were normal in shape and consistence; the cut surface revealed a normal architecture. There were multiple small cysts of the left ovary, approximating 2 or 3 mm. in diameter, and filled with clear, yellow fluid.

Examination of the polyp removed at operation showed it to be 4.3 by 3 by 1.8 cm. Cut section revealed a circular core, which was composed of tough connective tissue. Surrounding this was an abundant amount of glandular tissue. The mucosal epithelium was normal histologically. The lamina propria was markedly vascular, and there was extensive inflammatory cell infiltration consisting about equally of neutrophilic and eosinophilic polymorphonuclear leukocytes, plasma cells and mononuclear cells. At no part of the specimen was there any evidence of cancer.

CASE 6. A 16-year-old Negro boy born on the Outside Obstetrical Service of the Johns Hopkins Hospital had been observed throughout his life at frequent intervals in the various outpatient clinics and on the wards of the Johns Hopkins Hospital.

As far as could be determined, the family history was negative for bowel difficulties and for pigmentation of the type under discussion.

The patient had suffered all his life from complications attributed to intestinal polyposis. At the age of 8 months rectal prolapse with a visible polyp had occurred. This recurred repeatedly in spite of removal of several polyps—described grossly and histologically as "papilloma of the rectum."

At the age of 6 years, the boy began to have attacks of periumbilical pain about once a month. In 1946 he was admitted to the hospital for intussusception. A laparotomy was performed by Dr. H. William Scott, Jr. An ileocolic type of intussusception was found. Taxis was unsuccessful. Resection of the ascending colon, half the transverse colon and the ileum back 30 cm. from the beginning of the intussusception was performed. The ends of the colon and ileum were exteriorized by the Mickulicz technic and later closed. Two polyps were noted in the ileal portion of the operative specimen. There was no sign of melanosis coli in the specimen.

At the third admission, on June 11, 1947, because of dizziness and shortness of breath on exertion, the patient's diet was found to have been unusually inadequate, having consisted largely of candy and soft drinks. Physical examination revealed pallor and blowing systolic murmurs at the apex and in the pulmonic area. Examination of the blood disclosed a red-cell count of 3,420,000, with a hemoglobin of 4.3 gm., and a hematocrit of 19 mm., giving a mean corpuscular volume of 56 cubic microns, a mean corpuscular hemoglobin of 13 micromicrogm. and a mean corpuscular hemoglobin concentration of 23 per cent.

The stools gave negative to ++++ guaiac tests. No parasitic ova or cysts were identified. Preparations for sickling were repeatedly negative. After a detailed gastrointestinal study it was finally concluded that the patient probably had polyps somewhere in the alimentary canal, which our imperfect methods could not demonstrate, and that bleeding from these, together with a grossly inadequate diet, was responsible for the anemia. Lack of absorptive surface as a result of extensive intestinal resection was a possible additional factor. On iron therapy the reticulocytes rose to a peak of 12.8 per cent.

It was on this admission that attention was called to the pigmentary peculiarities and studies thereof were made. On the outside of both lips and extending onto the skin about 1.5 cm. from the vermilion border there were darkly pigmented spots of irregular outline and size varying from that

of a pinhead to 2 mm. in the largest dimension (Fig. 6). They covered the vermillion portions and the entire dental surfaces of the lips. There were a few similar spots on the buccal mucous membranes and lateral edges of the tongue. On the mucous membrane covering the posterior commissure of the upper and lower jaws there was on each side a prominent spot measuring about 4 mm. in diameter (Fig. 7). The general color of the skin was a very light tan. In the "butterfly area" of the face there were also a few spots resembling those on the lips (Fig. 6). There was a fleck of pigment in the bulbar conjunctiva of the right eye at the limbus at 8 o'clock, and a similar but small spot on the conjunctiva of the left eye at the limbus at 4 o'clock. Funduscopic examination revealed nothing remarkable. On the hypothenar

just below the ligament of Treitz, the region being intussuscepted into the jejunum below for a distance of 21 cm., and a second group of polyps approximately 61 cm. distal to Treitz's ligament. The jejunum was resected from the ligament of Treitz to below the second group, and an end-to-end



FIGURE 6. *Appearance of the Patient in Case 6.*
The characteristic dense localization of spots on the lips, more marked on the lower lip, is well demonstrated. Note the relative paucity of spots elsewhere on the face.

eminence of the right hand there was a pigmented spot 5 mm. in diameter. On both index fingers were numerous dots, and under the nail of the left index finger at the point a pigmented area (Fig. 8). There was a pigmented macule on the sole of the left foot. Otherwise the body was essentially free of any localized areas of increased pigmentation. All the areas described were not elevated and were perfectly smooth.

These areas of pigmentation had been present as long as the patient or his mother could recall and had not changed. Unfortunately, no photographs from infancy or childhood were available. One brother and 2 half sisters did not show the anomaly. None of the mother's family showed it; the father's family lived in a distant state and was not available for observation.

On May 25, 1948, the patient was admitted again with intussusception. On that date a laparotomy was performed by Dr. Marshall C. Sanford. Two groups of polyps were palpated in the small intestine: one in the upper jejunum



FIGURE 7. *Photograph Demonstrating Melanin Areas Inside the Mouth in Case 6.*

duodenojejunostomy performed. At this laparotomy a polyp was felt in the descending colon, and another in the sigmoid about 15 cm. below the first. After proper prepara-



FIGURE 8. *Photograph of the Right Hand in Case 6.*
Melanin spots are present on the palm and thumb and especially on the forefinger.

tion of the bowel with sulfasuxidine, a 15-cm. length of the left colon, including the polyps, was resected as a separate procedure on June 7. The polyps were grossly and microscopically identical with those previously removed.

CASE 7.* A 15-year-old girl had previously been admitted to the Johns Hopkins Hospital in 1937 at the age of 6 years. Eighteen months before that admission the patient had become rundown, pale and anorexic. One year before admission tarry stools were occasionally noticed, and there was the onset of dull abdominal pain present each morning on awakening. This daily morning pain continued until the time of the first admission, and, in addition, there was occasional nausea and vomiting. Sometimes, the pain required morphine for relief. During severe attacks it radiated to the left lower quadrant, where there was said to be a visible mass, and gurgling sounds were audible across the room. The stools were guaiac positive on numerous occasions, and the hemoglobin at one time was 30 per cent of normal.

On admission in 1937 the physical examination was recorded as essentially negative, and the diagnostic impression was Meckel's diverticulum. The spots in the mouth were described, but their diagnostic significance was not appreciated. Two days after admission the patient was seized with severe abdominal pain, which caused her to scream and clutch her abdomen. This was associated with continuous retching. On laparotomy 2 ileoileal intussusceptions and 3 polyps were discovered. The first intussusception was 45 cm. above the ileocecal valve and was easily reduced. A polyp was palpated at the head of the intussusceptum and was removed by elliptical resection. About 76 cm. above this intussusception was a second, larger one, which on reduction was found to be an intussusception within an intussus-



FIGURE 9. *Appearance of the Patient in Case 7.*
Note the spots on the lower lips and on the buccal mucosa. Spots are also visible on the mucosa just inside the nostril. Spots on the upper lip are relatively sparse.

ception with a polyp as the cause of each invagination. These polyps were similarly resected. No others were found.

The patient did well until the following spring, when she had an acute attack of abdominal pain and was operated upon in a South Carolina hospital, where adhesions were reported as the only finding. Thereafter she was well until 1946. During the next year there was a gradual loss of appetite, development of weakness and a loss of about 6 pounds of weight. Two months before this admission the old crampy abdominal pain recurred, lasting from 1 to 12 hours at a time. In the 2 weeks before admission in October, 1947, a steady

drop in hemoglobin to 60 per cent was observed. There was considerable nausea but no vomiting. Two days before, the patient had pain all day associated with considerable nausea but no vomiting.

On admission the physical findings were not remarkable except for the pallor (the hemoglobin was 9 gm.) and the spots described below. There was no digital clubbing. The stools were brown and formed, but guaiac positive. Sigmoidoscopic examination, performed by Dr. J. T. Howard, revealed 2 polyps in the lower sigmoid, 1 "the size of a peanut and the other the size of a hazelnut." A gastrointestinal series revealed negative filling defects in the stomach suggestive of polyps. Studies of the small intestine were performed by the passage of barium and then air through a Miller-Abbott tube inserted for the proper distance. By this method several areas suspicious of polyps were visualized. A barium enema by the routine technic and without injection of air was negative.

At operation, performed on October 31 by Dr. I. R. Trimble, the stomach was opened, and 2 polyps were found on the greater curvature in the lower portion of the organ. The larger of these measured about 2 cm. in diameter. The entire length of the small intestine was carefully examined by means of palpation and transillumination. In the distal jejunum and proximal ileum several polyps were palpated, and about 122 cm. of this portion of the gut was resected. This specimen contained 8 large pedunculated polyps, the largest of which measured about 25 cm. in diameter. Histologic examination revealed these structures to be typical benign polyps. Several polyps could be palpated in the transverse colon (the only portion of the large intestine in the operative field), but no operative procedure was attempted in connection with them.

The patient was an only child. Absolutely no history of gastrointestinal disturbance could be elicited among her forebears, nor had any of them, including the parents, shown a pigmentary anomaly resembling the patient's. These spots had been noted almost from birth. There was no family history of freckles. The mother had a photograph of the patient at the age of 3 months showing them quite distinctly. These spots were numerous on the vermilion border and on the dental aspect of the lips. They were perfectly flat areas of hyperpigmentation of irregular outline and variable size. On examination with a magnifying glass some of the spots had a somewhat stippled appearance. Spots of the same description were present on the buccal mucous membrane (Fig. 9) bilaterally, but none were seen on the tongue. There were several light spots over the palms and fingers, and there were a few on the feet. The remainder of the body was completely free of any unusual type of pigmentation. No freckles were present—in fact, the skin of the face was exceptionally free of all blemishes except the melanin spots described above.

CASE 8.† A 27-year-old man, second in a family of five the genealogy of which is shown in Figure 10, was a brother of the patients in Case 9 and 10. He was born in 1921. From an early age he has been subject to frequent, in fact almost daily, "bellyaches," especially after eating. Over the course of about 18 months, in 1938 and 1939, at the age of about 17, he had had some very severe attacks of crampy, intermittent abdominal pain, for which he was admitted to the Harrisburg Hospital on several occasions. Each time, the pain disappeared spontaneously, and no satisfactory diagnosis was arrived at. Finally, the possibility of intestinal polyposis, with intussusception, was proposed by Dr. C. E. Moore, who performed a laparotomy on December 18, 1939. At that time an easily reducible intussusception in the upper portion of the jejunum was discovered, and multiple soft masses could be felt in its lumen. About 150 cm. of jejunum was resected, extending from 10 cm. below the ligament of Treitz to below the area where polyps could be felt. End-to-side anastomosis was necessary because of luminal disproportion. The specimen removed was described by the pathologist as showing 30 soft, lobulated polyps. Microscopically, they were the usual adenomatous polyps.

Early in 1945, attacks of crampy abdominal pain began, mainly on the right, increasing in severity and frequency over the course of 3 months. On January 16, 1948, because of these increasingly severe attacks, laparotomy was per-

*This case is reported with the permission of Dr. I. R. Trimble. A report of this case is included in the paper by Ravitch¹² dealing with polypoid adenomatosis of the entire gastrointestinal tract.

†Case 8, 9 and 10 are reported through the courtesy of Dr. C. E. Moore, of Harrisburg, Pennsylvania.

formed. Two intussusceptions were discovered. The first was 90 cm. proximal to the ileocecal valve, with telescoping of the bowel for 10 cm. At the head of the intussusception was a thumb-sized polyp, which was removed by simple elliptical incision. The second intussusception was ileocolic in type and had its cause, again, in a small polyp the size of an English walnut. This was removed in a similar manner. A very careful examination of the entire gastrointestinal tract was made. No evidence of polyps was found in stomach, duodenum or jejunum, and on this occasion none could be felt in the colon, including the transverse colon, where it was thought that a solitary one had been felt in 1943. Histologically, the polyps were not remarkable.

After this operation the patient was asymptomatic up to the time when he was examined by one of us. He was found to be a very muscular young man, perhaps slightly

CASE 9. The sister (born in 1924) of the patients in Case 8 and 10, was 4th in a family of 5, the genealogy of which is shown in Figure 10. Through early adolescence the patient had suffered from recurrent attacks of crampy abdominal pain accompanied at times by vomiting. There was never melena or fresh blood in the stools, and she was never noticeably anemic. At the age of 16, because of this history and because of the previous discovery of polyposis in a brother (Case 8), she was admitted to the Harrisburg Hospital, and laparotomy was performed on June 28, 1940, by Dr. C. E. Moore. The upper 91 cm. of the jejunum was found to be somewhat dilated, and many firm nodules were palpated in its lumen, the most proximal one being about 8 cm. below the ligament of Treitz. No intussusception was present at the time of laparotomy. The stomach, duodenum, ileum and colon appeared to be normal. The proximal 90 cm.

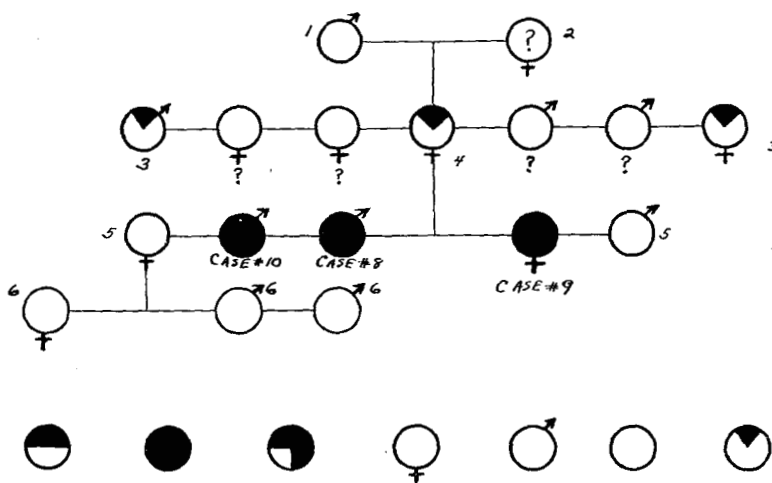


FIGURE 10. Genealogic Table of Harrisburg Family with Pigment Spots and Polyposis. (Data Provided through the Courtesy of Dr. C. E. Moore.)

Key: Blank circle = normal. One-fourth circle = pigmentation not looked for; probable polyposis. One-half circle = pigmentation; no polyps clinically. Three-fourths circle = pigmentation and probable polyposis. Full circle = pigmentation and proved polyposis.

1. Death from cancer of pancreas at age of sixty-nine. No pigmentation or intestinal polyps at autopsy.
2. No information available except death from "heart attack."
3. Death from "intussusception" in second decade of life. No information about pigmentation.
4. Death from "cancer of intestine" at age of forty. No information about pigmentation.
5. No history of pigmentation or intestinal trouble. Not available for examination. (See footnote under Case 10.)
6. No history of pigmentation or intestinal trouble. Not available for examination. (See footnote under Case 10.)
- ? No information available.

overweight. There was no evidence of anemia. The eyes were dark blue, and the hair brown black. The only unusual feature of the examination was the presence of gray pigmented spots on the vermillion border of the lower lip identical with those in the other cases. The spots were concentrated somewhat toward the commissure on either side. There were no spots on the dental aspects of the lips, but on the buccal mucosa in the region of the posterior commissures of the jaw, and in juxtaposition to the lower teeth there were small, irregular spots, which had a definite stippled appearance on magnification. There were two spots, likewise stippled, on the hard palate. (These spots had been noted from the first by Dr. Moore, who speculated on their possible relation to the intestinal polyposis). The face, which was deeply sun-tanned, was essentially free of freckles. The hands were rough and calloused, but a few small, brown-gray spots were seen on both dorsal and volar aspects of the fingers. The spots on the lips had been present and unchanged as long as the patient could recall.

of the jejunum was resected, and the continuity was restored by a lateral anastomosis. The specimen was found to contain 5 polyps, the largest measuring 3.5 cm. in length and 2.2 cm. in diameter. Histologically, they were the usual polypoid adenomas.

After operation the patient was asymptomatic. When examined by one of us in 1948, she was well developed and adequately nourished without evidence of anemia. She was somewhat darker in complexion than her brothers. The hair was black, and the irides dark brown. The only unusual feature of the physical examination consisted of dark, pigmented spots on the vermillion border of the lower lip, with a few smaller ones on the cutaneous portion of the lower lip. Those on the vermillion border were quite deeply pigmented and prominent, and only imperfectly concealed by lipstick. In the mouth there were 2 spots on the left buccal mucosa, 3 on the right and a single small pigmented area on the hard palate. All these areas had a definitely stippled appearance. There were a few spots in the butterfly area of the nose and

cheek. On both the dorsal and volar aspects of the fingers were a number of brown spots. The remainder of the body was free of unusual pigmentation.

CASE 10. The brother of the patients in Case 8 and 9 and 2nd in a family of 5, the genealogy of which is shown in Figure 10, experienced, at about the age of 20, recurrent attacks of mid-abdominal pain occurring especially between 1 and 2 hours after eating and occasionally accompanied by vomiting. The attacks increased in severity and frequency over the course of the next 2 years. In 1942 he was admitted to the Harrisburg Hospital with a particularly severe attack of this description of 2 days' duration. An indefinite tumescence was observed in the region of the umbilicus. At laparotomy, performed on February 16, by Dr. C. E. Moore, an intussusception was found in the jejunum about 76 cm. below the ligament of Treitz. This was quite easily reduced. At the head of the intussusception a polyp was palpated, and several others were felt in the jejunum to a distance of 122 cm. from the ligament of Treitz. The stomach, duodenum, ileum and colon felt normal. The jejunum was resected for a distance of 122 cm., beginning at a point 15 cm. below the ligament of Treitz. Lateral anastomosis was performed, the continuity of the bowel thereby being re-established.

After operation the patient had been completely asymptomatic up to the time he was examined by one of us in 1948. At that time he was found to be a very muscular, slightly overnourished young man with good color and a striking resemblance to his younger brother. The hair was dark brown, and the irides dark blue. In this case, the pigmentation of the lips was the least marked of any of the siblings. There were, however, over the vermilion border of the lower lip, 10 or 12 small dark-brown, pigmented spots concentrated mainly near the commissure on either side. Inside the mouth there were 2 or 3 pigmented spots with a stippled appearance on the buccal mucosa on each side. There was no pigmentation of the hard palate. The face was deeply tanned, but essentially free of freckles. The hands were calloused and roughened, but showed a few spots on the fingers.*

REVIEW OF THE LITERATURE

Interest in this syndrome was first aroused when a patient (Case 1) was seen on the Fifth Medical



FIGURE 11. Identical Twins, Each with Melanin Spots on and about the Lips and on the Buccal Mucosa, as Shown in the Small Insert. (Reproduced from Hutchinson.²)
Note the similarity of distribution of pigment spots in these cases with those reported in this paper.

Service of the Boston City Hospital in 1939 during a study of the association of skin pigmentation with systemic disease.¹ Dr. Chester S. Keefer, who

*On January 22, 1949, the youngest member of this Harrisburg family, a 21-year-old man, died a few days after admission to another hospital for an acute abdominal episode. Two operations were performed at which intussusception due to polyp of the small intestine was discovered. The brothers and sisters of this patient stated that he showed no pigmented spots, but he was actually not examined by us.

had seen the patient on ward rounds, commented later, in a personal communication, on the similarity of this girl's pigmentation to that of twins in the cases reported by Sir Jonathan Hutchinson² in 1896. This report concerned twelve-year-old twins (Fig. 11) with an anomaly described as follows:

... a number of black pigmented spots on the lips and inside of the mouth. It was at the age of three that these spots had first been noticed, and the evidence was definite that none had been present at birth. The spots had increased in number and size at exactly parallel rates in the two, and the conditions presented were just the same in each.

No note is made of the presence or absence of pigmented areas on the hands. The striking resemblance between the pigmentary pattern in Case 1 and the twins described by Hutchinson is clearly demonstrated by comparison of Figure 1 and Figure 11.

Hutchinson was not aware of the presence of any intestinal trouble in either of the twins, for he wrote further: "That they [the pigmented spots] are not in any active sense pathological we may safely assure, for they appear to be not aggressive, and their subjects remain in good health." Because of the marked similarity of the process in the twins Sir Jonathan considered the pigmentation a congenital anomaly.

A brief note on these twins had previously been published by Connor,³ who contributed the significant additional information that the twins were "of dark complexion and anemic." The pigment spots were described as being "of very small size and scattered over the lips (especially the lower), gums and hard palate, but not on the tongue."

The patient in Case 2 was seen at Boston City Hospital later in 1939 and because of similarity to Case 1 was likewise photographed and studied. This second case strongly suggested that this distinctive type of pigmentation in combination with intestinal polyposis was not a fortuitous association but was probably of related significance.

A limited search of the literature at that time revealed a paper by Weber,⁴ who in 1919 reported a follow-up study on Hutchinson's cases. He stated that the spots apparently had not enlarged. However, the most interesting portion of his follow-up observation was this: "One of the twins died at the age of twenty years, from intussusception, at the Metropolitan Hospital (London), but the other (B. H.) is still living and is in good health, now (1919) aged thirty-five years." The Metropolitan Hospital⁵ has no record that an autopsy was performed, a point confirmed by Weber.⁶ However, from a copy of the death certificate obtained for us by Dr. L. Forman, British dermatologist, it is known that an operation for intussusception with resection of the gut was performed and that the patient died of "septic pneumonia and pleuritis." Although not specifically stated there is a strong possibility that intestinal polyposis was the cause of the intussusception in the

first twin. A recent personal communication from R. H. (a living brother of the twins) states that the second twin died at the age of fifty-two of cancer of the breast. He could supply no data concerning intestinal symptoms. She died at home, and no autopsy was performed. Weber⁴ noted no pigmentation in the other members of the twin's family, a point corroborated by the brother, R. H.

Case 3 was called to our attention by Dr. Francesco Ronchese, of Providence, Rhode Island, after publication of the preliminary note concerning Case 1 and 2.¹

The patient in Case 4, a first cousin of another patient (Case 2), and still alive, came to our attention when relatives of the latter were questioned

and intestinal polyposis by a specific title is a paper by Peutz,⁷ of The Hague, who, in 1921, described a family in which several members had pigment spots of the mouth, hands and feet with intestinal polyposis. Reference to this paper is made by Meirowsky,⁸ and the article is also listed in the *Index Medicus* but was overlooked in our earlier, limited search.

No other title under the heading of intestinal polyposis with pigmentation was found in the *Quarterly Cumulative Index Medicus* or *Index Medicus* prior to 1945. Metzger, Ohlmann and Halff,⁹ under another title, reported a case of polyposis with a diffuse type of generalized melanin pigmentation that did not resemble the appearance

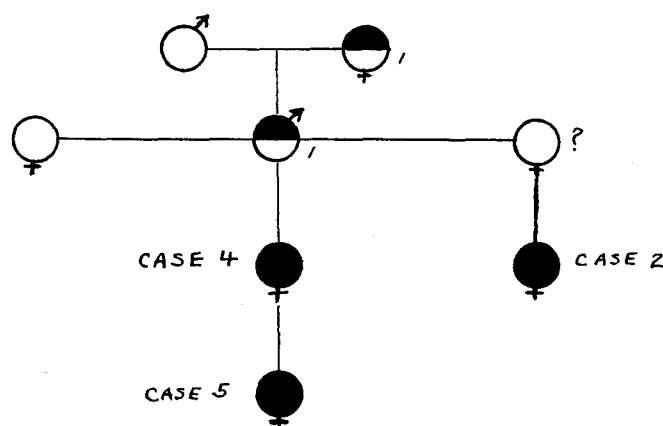


FIGURE 12. Genealogic Table of Boston Family with Pigment Spots and Polyposis.

1. Known to have characteristic pigmentation. No information about polyposis available.
? No information available.

about her family history. She had been admitted to Boston City Hospital in 1935. Adequate data were available in this record.

The patient in Case 4 gave the details for assembling the pedigree of the syndrome in this family (Fig. 12) and led to knowledge of her daughter (Case 5), who had died at the Children's Hospital, Boston, Massachusetts, in 1938.

Case 6 and 7 were noted by one of us at the Johns Hopkins Hospital within a few months of each other.

Case 8, 9 and 10 are patients of Dr. C. E. Moore, of Harrisburg, Pennsylvania, who, hearing of our interest in this syndrome, called them to our attention and permitted one of us to examine them.

The finding of 10 patients with this syndrome stimulated us to a more thorough search of the literature than the one made in 1944, when Case 1 and 2 were reported briefly.

Apparently the first specific reference in the medical literature concerning this disorder and the earliest to stress the association of pigmentation

in our cases. No mention of this syndrome was found in a representative group of standard textbooks on gastrointestinal disease, or in the standard dermatologic textbooks in English. This does not exclude the possibility that representative cases are reported under titles that would not suggest this syndrome.

As previously stated Peutz,⁷ of The Hague, in 1921, described a family in which several members had pigmented spots of the mouth, hands and feet. Dr. Peutz¹⁰ has very kindly supplied us with further information on this family, permitting the construction of the fabulous family tree shown in Figure 13. The cases cover three generations, with seven proved cases of the syndrome (intestinal polyps and spots), 1 suspected case and 1 person who presented the pigmentary anomaly without proved polyposis. Two of the family had nasal polyps in addition to the intestinal polyps, and 1 also had bladder polyps.

Figure 14 demonstrates the spots on the dental aspect of the lower lip in 1 of the cases (No. 7 in

obtained from Kisch,¹³ who reports that his original notes are no longer available. However, he confirmed the validity of the statement of Meirowsky.

Four proved and 2 probable cases of this syndrome came to our attention while we were reviewing the quite limited literature of familial adenomatosis of the small intestine.

In 1924 van Dijk and Oudendal,¹⁴ from Weltevreden in the Dutch East Indies, reported the cases of a sixteen-year-old Indo-European boy and his twenty-five-year-old sister, both of whom suffered from repeated colicky attacks. During severe attacks both were submitted to laparotomy and found to have intussusception of the ileum due to adenomas. Both patients showed pigmented spots of the lips, which had been present from birth and which resembled those found in our patients. The au-

been a patient in this hospital in 1935 complaining of attacks of abdominal pain, with the passage of blood and mucus per rectum." The subsequent course of events was as follows¹⁶: "This man was admitted to a nearby hospital in Cardiff during 1947 and laparotomy then showed an inoperable carcinoma of the stomach . . . no further history is obtainable at the moment."

Foster¹⁶ supplied information on a fourth very likely case of the syndrome in this Welsh family:

[The son of the patient just described] . . . was admitted to Llandough Hospital on the 7th of October 1944, as a case of Addison's disease apparently on account of the pigmentation of the lips, oral mucous membrane, and

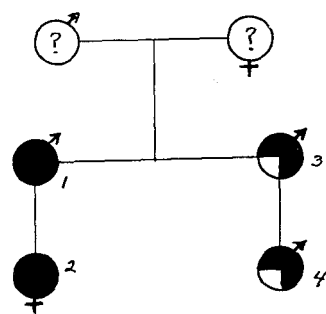


FIGURE 15. Genealogic Table of a Welsh Family with Pigment Spots and Polyposis. (Based on Data of Foster.^{14, 15})

1. Forty-three-year-old silversmith with spots and a proved polyp of the ileum.

2. Fifteen-year-old girl with spots and a proved polyp of the ileum.

3. Had the characteristic pigmentation and passage of blood and mucus by rectum. Inoperable carcinoma of the stomach developed.

4. Has the characteristic pigmentation as well as frequent attacks of colicky abdominal pain with passage of blood and mucus.

?No information available.

thors did not mention Peutz's publication of 1921 and did not stress the significance of the association of pigmented spots and intestinal polyposis.

In 1944 Foster¹⁵ reported the cases of a forty-three-year-old silversmith and his sixteen-year-old daughter who presented themselves at the Llandough Hospital in Cardiff, Wales, within three years of each other with intussusception, which on laparotomy was found to be due to a single polyp. Foster stated: "It was noted that both patients presented a diffuse brownish pigmentation of the lips and face." No further comment was made of the pigmentation. In reply to our inquiry Foster¹⁶ generously sent us a photograph of the daughter. The identity with the other cases is unmistakable.

In his report Foster¹⁵ stated: "On investigating the family history it transpired that the father's brother showed similar pigmentation, and he had



FIGURE 16. Appearance of a Patient with Melanin Spots. (Reproduced from Touraine and Couder¹⁸ with the Permission of the Publisher.)

This illustration clearly depicts the appearance of the melanin spots on the mucosa of the mouth.

palate. A history of attacks of abdominal pain of a colicky nature, occasionally severe and associated with the passage of blood and mucus per rectum over a period of about nine months was obtained. Since then he has had occasional attacks of abdominal pain with the passage of some mucus per rectum. . . .

Sufficient data were supplied by Foster for us to assemble a genealogic table for this family (Fig. 15).

The only other report of the complete syndrome was made by Touraine and Couder,¹⁷ of Paris, in 1945, under the title "Syndrome of Peutz," and elaborated upon in 1946 under the title "Lentiginose péri-orficielle et polypose viscérale."¹⁸ Their

patient was a fifteen-year-old girl with pigment spots of the lips and buccal mucosa (Fig. 16). The parents and a single sister were normal. In addition to the typical pigmentation, the patient had habitual constipation and occasional rectal prolapse with defecation. Rectal examination revealed an "enormous dilatation of the rectal ampulla and of the sigmoid; 7 cm. from the anus there was a mobile polyp, the size of a large nut, which, on biopsy, was a simple adenoma with great dilatation of the glandular cavities but without neoplastic transformation." A study adequate to exclude small-bowel polyposis was not made so that one can only speculate on its possible existence.

Touraine and Couder¹⁸ collected from the literature 31 cases of pigment pattern identical with that in the case described by them, by Peutz and by us. The term "lentiginose péri-orificielle" was used to describe the pigment portion of the syndrome. These cases occurred as follows: 22 cases were familial; 8 occurred in three generations

had been present occasionally, and examination of the blood demonstrated secondary anemia. No further data on studies of the gastrointestinal tract were given. Because of the death of Dr. Belote it was impossible to trace this case further.²¹

In 1912, Crouzon and Chatelin²² reported a case of the pigmentation in an eighty-three-year-old woman on the service of Pierre Marie at the Salpêtrière. In addition to the identical pigmentation, the patient was said to suffer from "rather frequent

TABLE 1. *Cases of Intestinal Polyposis and Pigmentation.*

TYPE OF CASE	AUTHOR	REPORTED IN LITERATURE	REPORTED BY PERSONAL COMMUNICATION
		NO. OF CASES	NO. OF CASES
Proved	Peutz ^{7, 10}	4	3
	van Dijk and Oudendal ¹²	2	
	Foster ¹⁴	2	
	Touraine and Couder ^{17, 18}	1	
	(only rectal polyps identified)		
Probable	Twin described by Hutchinson ^{2, 4, 6} (E. A. H.)		1
	Peutz ^{7, 10}	2	
	Foster ^{14, 15}	1	
Possible	Twin described by Hutchinson ^{2, 4, 6} (B. H.)	1	1
	Crouzon and Chatelin ²²	1	
	Hudelo and Rabut ²³	1	
	Belote ²¹	1	
Totals		16	5

(Peutz⁷); 5 in four generations (Siemens¹²) and 9 in three generations (Ferrari¹⁹). Our original report of 2 cases was apparently not available to Touraine and Couder and not included by them in this tabulation. (Its publication in a paper under the general title "Pigmentation of the Skin" made recognition through the index listing difficult.) They likewise were not aware of Foster's¹⁵ cases or those of van Dijk and Oudendal,¹⁴ probably because of the misleading titles of these two papers. As listed in this tabulation only the 4 cases of Peutz⁷ and possibly the one reported by Touraine and Couder^{17, 18} had the full syndrome.

It is of interest that in these various reports of the pigment pattern collected by Touraine and Couder¹⁸ 3 patients had data suggesting polyposis. Belote²⁰ reported at a dermatologic meeting the case of a twelve-year-old boy with the characteristic pigmentation who complained of bleeding from the rectum and increasing weakness; tarry stools



FIGURE 17. *Photograph of a Fifty-Seven-Year-Old White Woman Who Had Melanin Spots of Lips and Mucous Membrane of the Mouth but in Whom Polyps of the Stomach or Colon Were Not Demonstrated.*

This is a possible case of pigmentary portion of the syndrome without polyposis.

attacks of diarrhea (once or twice a month), not accompanied by vomiting."

The remaining suspected case of the syndrome was reported by Hudelo and Rabut²³ in 1927. Their patient manifested the characteristic pigmentation and in addition was said to have suffered from "indigestion, abdominal pains and nausea." Histologic study of a biopsy specimen revealed the pigment to be melanin.

The proved, probable and possible cases recorded in the literature or described in personal communications are summarized in Table 1.

Although one of us has been looking for such cases for the past eight years, we have personally encountered only 1 case in which a pigment pattern indistinguishable from that of the syndrome being discussed in this paper was noted in a person in whom polyposis could not be demonstrated. A brief report of this case* is as follows:

C. L., a 57-year-old woman from Pueblo, Mexico, was seen at the Johns Hopkins Hospital because of precordial pain, and was examined by one of us. The family history was negative for pigmentation, but intestinal trouble was present in the form of "strangulated hernia" in the maternal grandfather, chronic indigestion in a brother and fatal gastric hemorrhage in the father.

The patient was an obese woman with hypertension and typical angina pectoris. Intestinal complaints were denied. The pigmented spots of the lips and oral mucosa, which were similar to those in our other cases and are shown in Figure 17, had been present for at least 8 years and possibly longer. This point, however, was not too clearly established. The spots were located on the vermilion border of the lower lip, to a less extent of the upper lip, on the buccal mucosa and on the hard palate. There were a few small light spots on the palms and volar aspects of the fingers, but none were seen on the feet. The spots in and around the mouth varied in dimension from pin-point size to about 6 mm. in the largest measurement. They were brown black. On observation under magnification the spots had a definite, stippled appearance similar to that in Case 7, 8, 9 and 10.

Barium enema, including a double contrast air study, was negative, as were an upper gastrointestinal study and sigmoidoscopy. The stools were negative for occult blood. No special small-bowel study was made.

Because of the absence of gastrointestinal symptoms and negative studies, it was concluded that the patient probably did not have intestinal polyposis.

*We are indebted to Dr. R. Carmichael Tilghman for calling this case to our attention and for permission to publish it.

(To be concluded)

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